

Mesothelioma Clinical Pathways

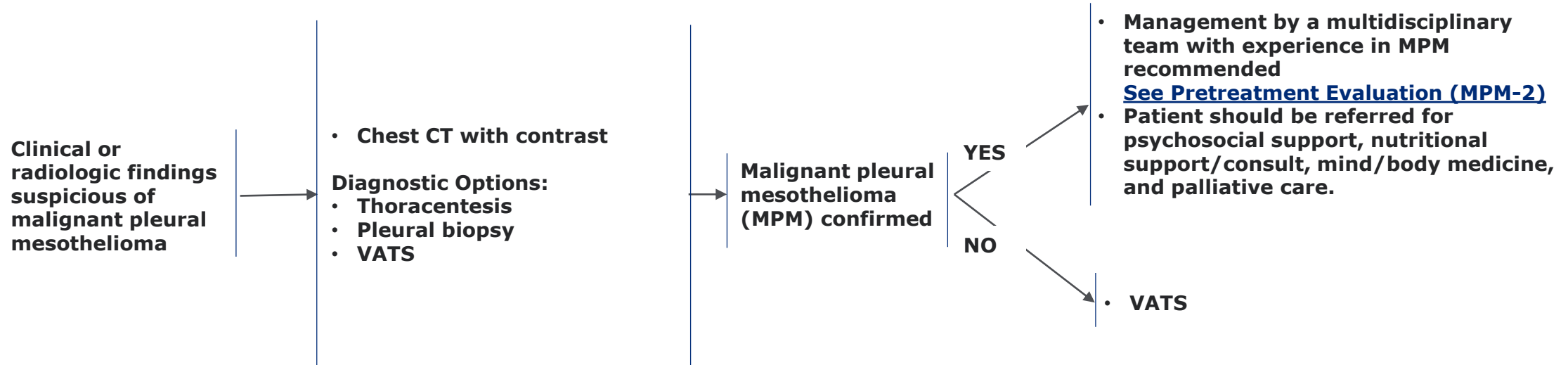
The following pathways have been developed through multidisciplinary efforts with physicians from the Mary Bird Perkins – Our Lady of the Lake Cancer Center. These pathways should be used as a supplemental guide for treatment for physicians at the Mary Bird Perkins – Our Lady of the Lake Cancer Center, and are not intended to replace the independent medical or professional judgment of physicians or other health care providers



*Approved by the Mesothelioma Specialty Treatment Team December 2016

Source: National Comprehensive Cancer Network. *Malignant Pleural Mesothelioma (Version 3.2016)*.
https://www.nccn.org/professionals/physician_gls/pdf/mpm_blocks.pdf.

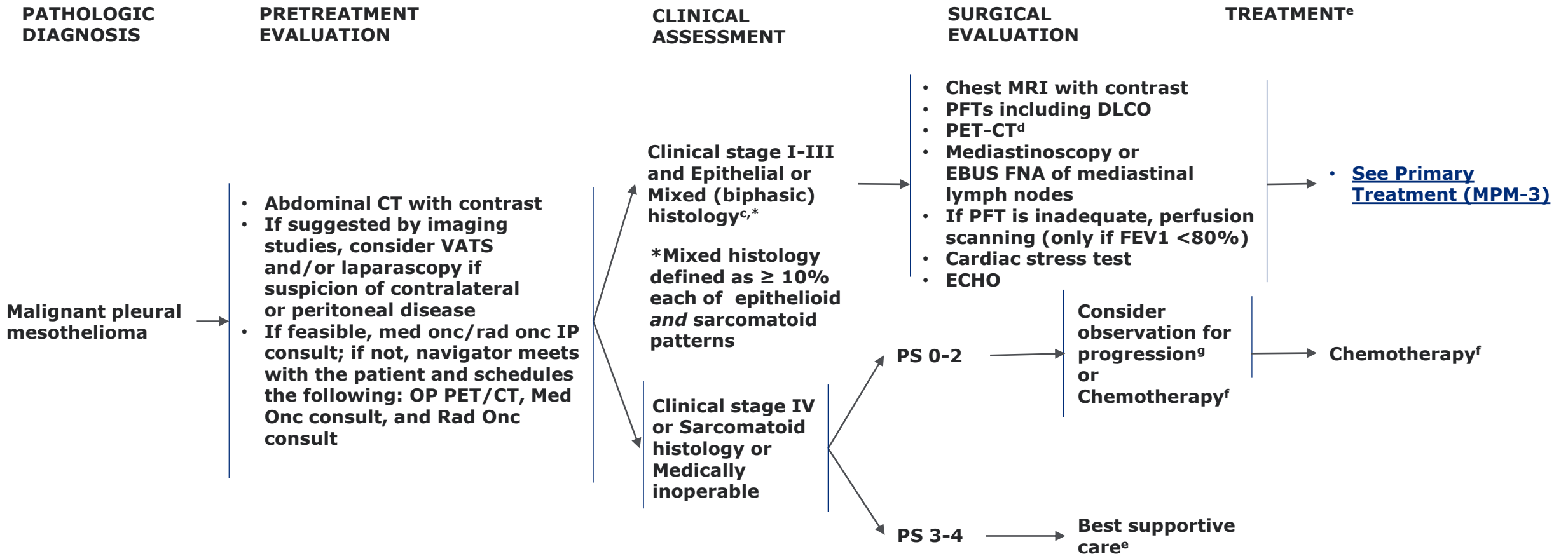
DIAGNOSTIC EVALUATION^a



^aThere are no data to suggest that screening improves survival

Note: All recommendations are category 2A unless otherwise indicated. NCCN believes that the best management of any cancer patient is in a clinical trial. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MPM-2



[See Evidence Blocks on MPM-B \(EB-1\)](#)

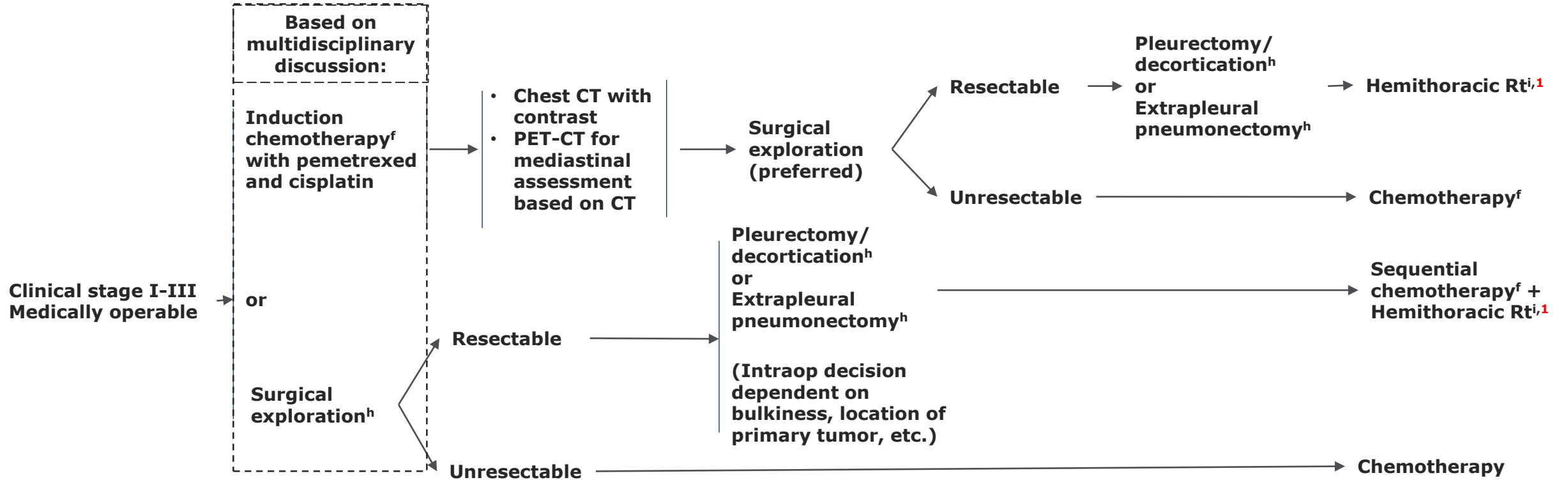
^aThere are no data to suggest that screening improves survival
^bFor further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
^cAssessment by multidisciplinary team with experience in malignant pleural mesothelioma
^dPET-CT should be performed before any pleurodesis
^e[See Principles of Supportive Care \(MPM-A\)](#)
^f[See Principles of Chemotherapy \(MPM-B\)](#)
^gObservation may be considered for patients who are asymptomatic with minimal burden of disease if chemotherapy is planned at the time of symptomatic or radiographic progression.

MPM-3

CLINICAL STAGE

PRIMARY TREATMENT^e

ADJUVANT TREATMENT



[See Evidence Blocks on MPM-B \(EB-1\)](#)

^eSee Principles of Supportive Care (MPM-A)

^fSee Principles of Chemotherapy (MPM-B)

^hSee Principles of Surgery (MPM-C)

ⁱSee Principles of Radiation Therapy (MPM-D)

¹Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma

PRINCIPLES OF SUPPORTIVE CARE

- Pleural effusions: Talc pleurodesis or pleural catheter, if required for management of pleural effusion^a
- Smoking cessation counseling and intervention (<http://www.smokefree.gov/>). [See the NCCN Guidelines for Lung Cancer Screening.](#)
- Pain management: [See NCCN Guidelines for Adult Cancer Pain](#)
- Nausea/vomiting: [See NCCN Guidelines for Antiemesis](#)
- Psychosocial distress: [See NCCN Guidelines for Distress Management](#)
- [See NCCN Guidelines for Palliative Care](#) as indicated

^aRecommend obtaining PET/CT before pleurodesis. Confirm diagnosis of malignant pleural mesothelioma (MPM) prior to pleurodesis. If MPM is suspected, consider evaluation by a multidisciplinary team with expertise in MPM.

5					E = Efficacy of Regimen/Agent
4					S = Safety of Regimen/Agent
3					Q = Quality of Evidence
2					C = Consistency of Evidence
1					A = Affordability of Regimen/Agent
	E	S	Q	C	A

PRINCIPLES OF CHEMOTHERAPY (1 of 2)




FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- Pemetrexed* 500 mg/m² day 1
Cisplatin 75 mg/m² day 1
Administered every 3 weeks (category 1)¹
- Pemetrexed 500 mg/m² day 1
Cisplatin 75 mg/m² day 1
Bevacizumab 15 mg/kg day 1
Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression^{2,**}
- Pemetrexed* 500 mg/m² day 1
Carboplatin AUC 5 day 1
Administered every 3 weeks³⁻⁵
- Gemcitabine 1000–1250 mg/m² days 1, 8, and 15
Cisplatin 80–100 mg/m² day 1
Administered in 3- to 4-week cycles^{6,7}
- Pemetrexed* 500 mg/m² every 3 weeks⁸
- Vinorelbine 25–30 mg/m² weekly⁹

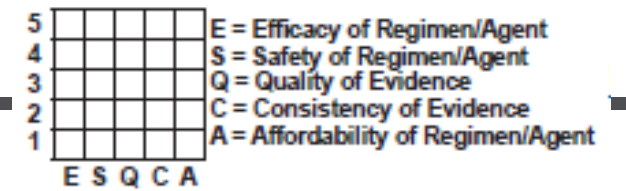
*Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma and tunica vaginalis testis mesothelioma.¹⁶

**The combination regimen of pemetrexed/cisplatin/bevacizumab is only for unresectable disease.

SECOND-LINE CHEMOTHERAPY

- Pemetrexed* (if not administered as first-line) (category 1)¹⁰ 
Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted¹¹
- Vinorelbine^{12,13} 
- Gemcitabine¹³⁻¹⁵ 

[See Evidence Blocks for First-Line Therapy on MPM-B \(EB-1\)](#)



EVIDENCE BLOCK FOR FIRST-LINE CHEMOTHERAPY

	Clinical stage IV, sarcomatoid, or medically inoperable MPM PS 0-2 (MPM-2)	Induction chemotherapy for medically operable clinical stage I-III (MPM-3)	Unresectable clinical stage I-III (MPM-3)	Postoperative chemotherapy for clinical stage I-III not receiving induction therapy (MPM-3)
Carboplatin + pemetrexed		—		
Cisplatin + gemcitabine		—		
Cisplatin + pemetrexed				
Cisplatin + pemetrexed + bevacizumab followed by maintenance bevacizumab		—		—
Pemetrexed		—		
Vinorelbine		—		

PRINCIPLES OF CHEMOTHERAPY (2 of 2)

References

- ¹Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636-2644.
- ²Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2015 Dec 21. [Epub ahead of print]
- ³Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma. *Ann Oncol* 2008;19:370-373.
- ⁴Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol* 2008;24:1443-1448.
- ⁵Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma. *J Thorac Oncol* 2008;3:758-763.
- ⁶Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491-496.
- ⁷Van Haarst JM, Baas J, Manegold CH, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002; 86:342-345.
- ⁸Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. *J Thorac Oncol* 2008;3:764-771.
- ⁹Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685-1694.
- ¹⁰Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008;26:1698-1704.
- ¹¹Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. *Lung Cancer* 2012;75:360-367.
- ¹²Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009;63:94-97.
- ¹³Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung Cancer* 2014;84:271-274.
- ¹⁴Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005;16:923-927.
- ¹⁵van Meerbeeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer* 1999;85:2577-2582.
- ¹⁶Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agents. *Lung Cancer* 2009;64:211-218.

PRINCIPLES OF SURGERY¹

- **Surgical resection should be performed on carefully evaluated patients by board-certified thoracic surgeons with experience in managing MPM.**
- **For patients being considered for surgery, a single-port thoracoscopy on the line of the potential incision is recommended.**
- **The goal of surgery is complete gross cytoreduction of the tumor. The goal of cytoreductive surgery is “macroscopic complete resection.” In other words, removal of ALL visible or palpable tumors. In cases where this is not possible, such as in multiple sites of chest wall invasion, surgery should be aborted. If it is possible to remove most of the gross disease to help with postoperative management, with a minimal impact on morbidity, then surgery should be continued.**
- **The surgical choices are: 1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor; and 2) extrapleural pneumonectomy (EPP), which is defined as en-bloc resection of the pleura, lung, ipsilateral diaphragm, and often pericardium. Mediastinal node sampling should be performed with a goal to obtain at least 3 nodal stations.**
- **Numerous studies have defined sarcomatoid as a poor prognostic factor for any surgical or non-surgical treatment of MPM and is a contraindication to EPP.**
- **For early disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid), PD may be safer than EPP but it is unclear which operation is oncologically better. There is controversy regarding choice of procedure that needs to be weighed, taking into account tumor histology, distribution, patient pulmonary reserve, and availability of adjuvant and intraoperative strategies. P/D and EPP are each reasonable surgical treatment options and should be considered in select patients for complete gross cytoreduction.²⁻⁵**
- **If N2 disease or a mixed histology tumor is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.**
- **If technically appropriate for even more advanced disease, lung sparing operations like P/D reduces the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection.**
- **Intraoperative adjuvant therapy, such as heated chemotherapy or photodynamic therapy, is still under investigation but may be considered as part of a reasonable multidisciplinary approach to this locally aggressive disease.**
- **After recovery from surgery, patients should be referred for adjuvant therapy, which may include chemotherapy and RT depending on whether any preoperative therapy was used and on the pathologic analysis of the surgical specimen.**

¹Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: A consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol* 2011;6:1304-1312.

²Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008;135:620-626.

³Spaggiari L, Marulli G, Boyolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. *Ann Thorac Surg* 2014;97:1859-1865.

⁴Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. *J Thorac Oncol* 2010;5:1649-1654.

⁵Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011;12:763-772.

PRINCIPLES OF RADIATION THERAPY (1 of 3)

General Principles

- Recommendations regarding RT should be made by a radiation oncologist.
- The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed in a multidisciplinary team, including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- For patients with resectable MPM who undergo EPP, adjuvant RT can be recommended for patients with good performance status (PS) to improve local control.¹⁻⁶
- PET scanning for treatment planning can be used as indicated.
- RT can be used to prevent instrument-tract recurrence after pleural intervention.
- RT is an effective palliative treatment for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with mesothelioma.
- When there is limited or no resection of disease, delivery of high-dose RT to the entire hemithorax in the setting of an intact lung has not been shown to be associated with significant survival benefit, and the toxicity is significant.^{1,5,6} RT under such circumstances or after P/D is usually not recommended, but may be considered with caution under strict dose limits of organs at risk or IRB-approved protocols.
- Acronyms and abbreviations related to RT are the same as listed in the principles of RT for non-small cell lung cancer.

[See NCCN Guidelines for Non-Small Cell Lung Cancer.](#)

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment.
[See Recommended Doses for Conventionally Fractionated Radiation Therapy \(MPM-D 2 of 3\).](#)
- The dose of radiation for adjuvant therapy following EPP should be 50–60 Gy in 1.8–2.0 Gy based on the margin status. A dose of 54 Gy given to the entire hemithorax, the thoracotomy incision, and sites of chest drains was well-tolerated.^{6,7} When it is challenging to deliver 50 Gy, every effort should be made to deliver a minimum dose of 40 Gy.¹
- A dose ≥ 60 Gy should be delivered to macroscopic residual tumors if the doses to adjacent normal structures are limited to their tolerances. In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall.⁸⁻¹⁰
- Daily doses of 4 Gy appear to be more efficacious than fractions of less than 4 Gy in providing relief from chest pain associated with mesothelioma,^{9,11} although the optimal daily and total dose of RT for palliative purposes remains unclear.
- For prophylactic radiation to surgical sites, a total dose of 21 Gy (3 x 7 Gy) is recommended.^{8,12} For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam radiation in combination with surgery.

[See Radiation Techniques \(MPM-D 2 of 3\)](#)

[See References \(MPM-D 3 of 3\)](#)

PRINCIPLES OF RADIATION THERAPY (2 of 3)

Recommended Doses for Conventionally Fractionated Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
Postoperative after EPP	50–54 Gy	1.8–2 Gy	4–5 weeks
Negative margins	54–60 Gy	1.8–2 Gy	5–6 weeks
Microscopic-macroscopic positive margins			
Palliative	20–40 Gy	≥4 Gy	1–2 weeks
Chest wall pain from recurrent nodules	or 30 Gy	3 Gy	2 weeks
Multiple brain or bone metastasis	30 Gy	3 Gy	2 weeks
Prophylactic radiation to prevent surgical tract recurrence	21 Gy	7 Gy	1 week

[See General Principles and Radiation Dose and Volume \(MPM-D 1 of 3\)](#)

[See References MPM-D \(3 of 3\)](#)

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤1; good functional pulmonary status; good function of contralateral kidney confirmed by renal scan; and absence of disease in abdomen, contralateral chest, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.

Radiation Techniques

- Use of conformal radiation technology is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.
- CT simulation-guided planning using either intensity-modulated radiation therapy (IMRT) or conventional photon/electron RT is acceptable.⁷ IMRT is a promising treatment technique that allows for a more conformal high-dose RT and improved coverage to the hemithorax. IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol. When IMRT is applied, the NCI and ASTRO/ACR IMRT guidelines should be strictly followed.^{13,14} Special attention should be paid to minimize radiation to the contralateral lung,¹⁵ as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.¹⁶ The mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.¹⁷
- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
- The clinical target volume (CTV) for adjuvant RT after EPP should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
- Extensive elective nodal irradiation (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
- The planning target volume (PTV) should consider the target motion and daily setup errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

PRINCIPLES OF RADIATION THERAPY (3 of 3) - References

- ¹Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2005;63:1045–1052.
- ²Gupta V, Krug LM, Laser B, et al. Patterns of local and nodal failure in malignant pleural mesothelioma after extrapleural pneumonectomy and photon-electron radiotherapy. *J Thorac Oncol* 2009;4:746–750.
- ³Bölükbas S, Manegold C, Eberlein M, et al. Survival after trimodality therapy for malignant pleural mesothelioma: Radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. *Lung Cancer* 2011;71:75–81.
- ⁴Hasani A, Alvarez JM, Wyatt JM, et al. Outcome for patients with malignant pleural mesothelioma referred for trimodality therapy in Western Australia. *J Thorac Oncol* 2009;4:1010–1016.
- ⁵Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 1997;63:334–338.
- ⁶Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg* 2001;122:788–795.
- ⁷Yajnik S, Rosenzweig KE, Mychalczak B, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2003;56:1319–1326.
- ⁸Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. *Chest*. 1995;108:754–758.
- ⁹de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura—a single-institution experience with 189 patients. *Int J Radiat Oncol Biol Phys* 1999;43:511–516.
- ¹⁰de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. *Chest* 2002;121:480–487.
- ¹¹Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: review of a 5-year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990;13:4–9.
- ¹²Di Salvo M, Gambaro G, Pagella S, et al. Prevention of malignant seeding at drain sites after invasive procedures (surgery and/or thoracoscopy) by hypofractionated radiotherapy in patients with pleural mesothelioma. *Acta Oncol* 2008;47:1094–1098.
- ¹³Moran JM, Dempsey M, Eisbruch A, et al. Safety considerations for IMRT: executive summary. *Med Phys* 2011;38:5067–5072.
- ¹⁴Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT). *Int J Radiat Oncol Biol Phys* 2009;73:9–14.
- ¹⁵Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 2007;84:1685–1692; discussion 1692–1693.
- ¹⁶Allen AM, Czerminska M, Jänne PA, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. *Int J Radiat Oncol Biol Phys* 2006;65:640–645.
- ¹⁷Krayenbuehl J, Oertel S, Davis JB, Ciernik IF. Combined photon and electron three-dimensional conformal versus intensity-modulated radiotherapy with integrated boost for adjuvant treatment of malignant pleural mesothelioma after pleuropneumonectomy. *Int J Radiat Oncol Biol Phys* 2007;69:1593–1599.